Noon

1059-20 **Does Elevating Catecholamine Concentrations Impact the Defibrillation Threshold?**

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Background: The defibrillation threshold (DFT) is important for setting defibrillation energy of implanted cardioverter-defibrillators (ICD). DFT is determined under anesthesia, which lowers circulating catecholamines. Whether DFT is impacted by epinephrine (EPI), an alpha-1, beta-1 and beta-2 receptor stimulator, and norepinephrine (NOREPI), a beta- and alpha-1 receptor stimulator, is unknown. Also, concomitant beta-blockers (BBLs) may alter DFT effects of catecholamines. Our objective was to determine the impact of elevated EPI or NOREPI concentrations on DFT in ICD patients with and without concomitant cardioselective BBLs. Methods: DFT testing was performed per a step-down protocol. Once routine DFT was determined, patients (n = 50, 64.8 ± 13.1 yrs, 72% male, 70% CAD, EF = 35.8 ± 15.5%) were stratified by use of cardioselective BBLs (n=30) or no BBLs (n=20) and randomized to an intravenous infusion of EPI, NOREPI or placebo (2mcg/min). After achieving steady state (7 min), the DFT was confirmed by repeat testing (experimental DFT). Results: NOREPI reduced DFT in the BBL (p=0.037) and no BBL (p=0.076) groups. The direction of EPI's effect on DFT depended on use of concomitant BBLs. In the EPI group, those on BBLs experienced a negative DFT change from baseline and DFT change in those not on BBLs was positive (-1.5 ± 2.4 vs. +2.0 ± 4.6, p=0.029). DFT was unchanged with placebo. Conclusion: NOREPI decreases DFT, possibly by alpha stimulation, and the effect of EPI on DFT differs depending on BBL use.

Effect of Catecholamines on DFT

Group	Routine DFT	Experimental DFT	p-value
BBL + Norepi (n=10)	9.5 ± 4.4	7.5 ± 3.5	0.037
No BBL + Norepi (n=6)	10.0 ± 3.2	7.5 ± 4.2	0.076
BBL + Epi (n=10)	8.0 ± 2.6	6.5 ± 2.4	0.081
No BBL + Epi (n=7)	10.4 ± 4.8	12.4 ± 7.0	0.296
Placebo (n=17)	9.4 ± 3.5	8.5 ± 3.9	0.332

Noon

1059-21 **Skeletal Myoblast Transplantation Through a Catheter-Based Coronary Sinus Approach: An Effective Means of Improving Function of Infarcted Myocardium**

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Whereas the *feasibility* of percutaneous techniques of cell delivery has been established, evidence for their *functional efficacy* still remains scarce. Because the transvenous approach is relatively simple, we first undertook an *histological* study which showed the ability of this route to achieve a successful engraftment of skeletal myoblasts into target scars. The present experiments were designed to assess the *functional* relevance of these findings. An anterior myocardial infarction was induced in 12 sheep by the release of a thrombogenic coil in the left anterior descending coronary artery. Simultaneously, a muscle biopsy was harvested and expanded. Two weeks later, left ventricular (LV) function was assessed by echocardiography and sheep were instrumented percutaneously with a dedicated catheter (TransAccess^{TM}, Transvascular, Menlo Park, CA) which incorporates a tipped phase-array ultrasound probe for guidance and an extendable needle for puncture of the venous wall. A microcatheter is then advanced through the needle into the infarcted tissue and used for cell delivery. Following the baseline echo, sheep were randomly allocated to receive 4 staged in-scar injections of either autologous cells (200 to 250 x 10^6 in 8 mL, of which _ 80% were myoblasts identified by a positive staining for CD 56, n = 6) or an equivalent volume of culture medium (n = 6). There were no acute postinjections complications like pericardial blood effusion or arrhythmias. Two months later, LV function was reassessed blindly and hearts were explanted for subsequent immunohistochemical analysis. Baseline LV ejection fraction (EF) did not differ between control and transplanted sheep (59.4 ± 8.1 % and 56.1 ± 10.6 %, mean ± SEM, respectively). Two months later, LVEF was significantly higher in the transplanted group (72.6 ± 3.4 % *vs* 50.4 ± 3.4 % in controls, $p = 0.02$). This improvement was primarily related to a decrease in systolic volumes following myoblast transfer (11.1 ± 4.4 cm^3 *vs* 30.8 ± 3.1 cm^3 in controls, $p = 0.07$) whereas diastolic volumes did not differ between the 2 groups. These data suggest the functional efficacy of the transvenous coronary sinus technique as a less invasive means of cell delivery to infarcted myocardium.

Noon

1059-22 **Cardiomyogenic Stem Cells in Human Bone Marrow**

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Introduction: Rodent bone marrow mesenchymal stem cells have been reported to transdifferentiate into cardiomyogenic cells. However, there is little evidence to support the existent of cardiomyogenic progenitors in human bone marrow.
Methods: Sternum bone marrow cells from 15 patients undergoing coronary artery bypass surgery were enriched for mesenchymal stem cells by negative immuno-selection against CD3, CD14, CD19, CD38, CD66b and GlyA markers. The enriched cells were separated in Ficoll gradient and cultured with DMEM until fibroblastic colonies were formed. The cells were expanded in differentiation medium with specially selected serum and plated into tissue culture dishes at 10^4cells/cm^2. After 5 days, the cells were stained with antibodies against alpha smooth muscle actin (SMA), CD44, CD45, CD90, CD105/SH2, CD106 and CD117 to confirm the identity of mesenchymal stem cells. Antibodies against cardiac troponin I, cardiac troponin T, alpha/beta cardiac myosin heavy chain (α/β MHC), sarcomeric tropomyosin, alpha-actinin, alpha-actin, titin and sarcoplasmic or endoplasmic reticulum calcium ATPase 2 (SERCA2) were used to detect the presence of cardiomyogenic cells.
Results: Immunohistochemical analyses revealed that about 1% of the cells in the colonies were positive for troponin I in the unpassaged cultures. Approximately 80-90% of the cells were stained positive for troponin I, α/β MHC, titin, tropomyosin, alpha-actinin, alpha-actin, SERCA2 but negative for troponin T after 1 to 3 passages in differentiation medium. Some nascent myofibrillar structures were observed in the cells. These myogenic cells also stained positive for SMA, CD44, CD90, CD105/SH2 and CD106 but negative for both CD45 and CD117.
Conclusion: Human adult bone marrow possesses a subpopulation of mesenchymal stem cells with cardiomyogenic lineage that are expandable with a specific culture condition. This holds great promise for their use in cellular therapy to repair damaged myocardium.

Noon

1059-23 **Cell Location May Be a Primary Determinant of Safety After Myoblast Transplantation Into the Infarcted Heart**

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*Introduction :*Arrhythmic complications associated with transplanting autologous myoblasts into infarcted myocardium can be fatal. The creation of an animal model to identify the vulnerability of the myocardium to this phenomenon might assist in identifying factors that contribute to these events. We hypothesize that cell location may be a primary factor in the production of arrhythmias.
Methods: Fourteen days after LAD ligation, 1e8 myoblasts were injected into the center (n=3; sham,n=1) or border zone (n=6; sham,n=2) of infarcted LV. A total of 1415 hrs continuous Holter monitoring was performed in 24 hr blocks at BASELINE (prior to injury) (250 hrs), POST MI (288 hrs) and at 3 day intervals after therapy (877 hrs) until death or 30 day endpoint.
Results: BASELINE Holters showed occasional atrial and ventricular dysrhythmia including premature atrial complexes. POST-MI animals showed new PVCs, couplets, and in 1 animal, sustained monomorphic V-tach. Hyperacute S-T elevations were seen in one animal POST MI and in one post sham injection. New dysrhythmias were not observed in the other sham injections . After border zone injection of myoblasts, one or more of the following were documented over serial recordings in each animal: more frequent and polymorphic PVCs, faster and more aggressive couplets, triplets, more prolonged post-PAC pauses, and bradycardic death, with a tendency for dysrhythmias to appear 6-9 days after cell injection. After cell injection into the center of the scar arrhythmias were less-frequent and less-aggressive.
*Conclusion:*1. In rabbits, conduction abnormalities and supraventricular arrhythmias exist at baseline 2. Post-MI; new dysrhythmias, especially monomorphic PVCs are commonly observed. 3. Myoblast injection into the border zone of an infarct appears to lead to more erratic and aggressive ventricular ectopy, conduction recovery delay and lethal bradycardia compared to central scar injection. This rabbit model suggests location of cells injected into myocardial scar may play a role in subsequent electrical vulnerability.

Noon

1059-24 **Physical Activity Attenuates the Risk of Stroke in Middle-Age Men With Left Ventricular Hypertrophy: 40-Year Follow-Up (1961-2001) of the Corfu Cohort (Seven Countries Study)**

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Background. We investigated the interaction between physical activity and left ventricular hypertrophy (LVH) on stroke mortality, based on 40 years follow-up of the Corfu cohort (Seven Countries Study). Methods. The population studied consisted of 529 rural men (40 – 59 years old) enrolled at 1961. LVH was electrographically confirmed. Activity levels were assessed by self-reports of habitual, occupational and leisure time physical activities. Cox proportional hazards models were used to assess the investigated parameters. Results.During the 40-year follow up, 461 (87%) died, 74 (16%) of these deaths were due to stroke. LVH was present in 40 individuals. Three hundred and sixty-two (68%) men were defined as physically active. High fitness (>4 Kcal/min) was associated with 35% lower risk of stroke (hazard ratio = 0.65, p<0.05), while the presence of LVH increased the risk 5-fold (hazard ratio = 5.24, p<0.001). Multivariate analysis controlling for several potential confounders revealed that increased fitness (>7 Kcal/min), attenuated the risk of stroke by 24% (hazard ratio = 0.76, p = 0.008) in those with LVH. Conclusion. LVH is a dominant characteristic of stroke mortality. Increased physical activity levels are associated with significantly lower stroke mortality in men with and without LVH.